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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	:	
ROSARIO LIZIO, ET AL.	:	EXAMINER: WESTERBERG, N. M.
SERIAL NO: 10/564,096	:	
FILED: MAY 2, 2006	:	GROUP ART UNIT: 1618
FOR: MULTIPARTICLE PHARMACEUTICAL DOSAGE FORM CONTAINING A MUCOADHESIVELY FORMULATED PEPTIDE OR PROTEIN ACTIVE SUBSTANCES METHOD FOR PRODUCING SAID PHARMACEUTICAL DOSAGE FORM	:	

APPEAL BRIEF

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

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(i) Real Party in Interest

Evonik Röhm GmbH is the real party in interest.

(ii) Related Appeals or Interferences

The Appellants are unaware of any related appeals or interferences that would directly affect, be directly affected by, or have a bearing on the Board's decision in this appeal.

(iii) Status of the Claims

Claims 1, 3, 4, 6-10 and 33-35 are on Appeal. Claims 1 are the only independent claims on Appeal.

Claims 2, 5 and 11-32 have been withdrawn from consideration.

No claims have been cancelled.

The Claims Appendix below provides a clean copy of the claims on appeal entered by the Amendment filed January 29, 2009.

(iv) Status of the Amendment

The Amendment filed on January 29, 2009 has been entered for purposes of Appeal (see the Advisory Action dated February 17, 2009).

(v) Summary of the Claimed Subject Matter

The invention provides superior targeted release of active peptide components, such as cetrorelix (a decapeptide), the elected species of active ingredient. The active ingredient is incorporated into "an inner matrix layer" that also contains a mucoadhesive polymer, such as chitosan. The inner matrix layer is contained within an "outer film" consisting essentially of an anionic polymer or copolymer. The elected species is anionic (meth)acrylate copolymers (e.g. EUDRAGIT) L type. The Appellants previously elected compositions that do not contain a separating layer between the inner matrix and outer film, and compositions lacking a biophilic matrix.

The outer film protects the peptidic active ingredient in the inner matrix layer, for example, from digestion in the stomach (specification, page 4, lines 10-16). Peptide-like drugs are destroyed or inactivated by digestion in the stomach (specification, page 2, line 10-11). By providing an outer coating that dissolves, for example, after passage through the stomach, high amounts of the active peptidic component contained in the inner matrix can be released at a desired site, e.g., in the intestinal lumen.

Once the outer coating dissolves and the inner matrix containing the active ingredient is released (specification, page 6, lines 6-19), the mucoadhesive component of the inner matrix provides superior bioavailability compared to prior art timed-release preparations containing bioadhesive components (instead of mucoadhesive ones) which reduce mucosal binding since they bind to other biological molecules. The residence time of mucoadhesives that bind to mucus or mucin differs from the residence time of bioadhesives that bind to non-mucosal biological components such as cellular membranes.

Moreover, mucoadhesives lack the toxicity of bioadhesive pellets or particles, because they are removed by the natural turnover of mucus and thus have lower residence times than bioadhesive compounds like gelatin that bind to cells and expose the cells for longer periods

of time to irritating drugs. On the other hand, mucoadhesive pellets/particles that bind to mucus/mucin do not exhibit the potential toxicity of bioadhesive particles binding directed to cells, because they bind to and distribute within mucous which provides a natural barrier to harmful components. For example, bacteria that are bound by mucus and which do not have bioadhesive properties (e.g., by cell binding proteins, pili, etc.) are washed off the mucosal surface. Similarly, the mucoadhesive properties of the invention limit the residence time of pharmaceutical agents and reduce toxicity and side-effects, while use of corresponding bioadhesive compounds like gelatin increase exposure time and side-effects.

Thus, unlike prior art compositions using bioadhesive components that are removed from mucous by binding directly to cells and which can exhibit toxicity because of this binding, the invention provides good distribution of the active ingredient in the intestinal lumen (specification, page 33, lines 29-30) to provide for targeted release of the active peptidic agent in the "intestinal mucosa" (specification, page 6, lines 17-19).

The present invention stands for targeted release of a **mucoadhesive** inner matrix containing an active ingredient as opposed to agents that are merely **bioadhesive** and adhere to biological components other than mucous. Chitosan is one such mucoadhesive component and in the invention it is formulated to exert these mucoadhesive properties, that is, to specifically bind to the intestinal mucosa and release the active substance there (see the top of page 5 of the specification). As required by claim 1 the "mucoadhesive matrix layer is exposed and binds to the intestinal mucosa and releases the active substance there".

Gelatin, a bioadhesive component, is the main ingredient in prior art compositions, such as thos of Watts discussed in the arguments below. These types of bioadhesive compositions will bind in first place to the glycocalyx membrane—that is particpate in "bioadhesive" binding in contrast to "mucoadhesive" binding. "Bioadhesive" means binding to the glycocalyx membrane but not to the mucus. This has the disadvantage that the

particles are stuck or glued to glycocalyx of the intestine cells. This is undesirable because binding to the glycocalyx may cause irritation of the cells and unwanted pharmacological side effects. Moreover, the addition of gelatin at least diminishes the beneficial effects of mucosal binding by chitosan and mucosal release of the active substance since the glycocalyx will be covered by gelatin complexes.

The present invention avoids these disadvantageous effects since mucosal-targeted complexes bound to the mucus can be washed away after the release of the active ingredient by the natural, on-going, renewal of the mucus layer. Further description of bioadhesive binding of gelatin to glycocalyx membrane is provided by WO 93/13753 at page 28, line 33-page 29, line 2 and at page 13, lines 14-23 and Fig. 3.

Annotations showing support in the original claims or specification are **embolded** and indicated inside [**brackets**] below:

Claim 1: An oral multiparticulate pharmaceutical form [**claim 1, line 1**] comprising pellets having a size in the range from 50 to 2,500 μm [**claim 1, line 3**], which comprise:

a) an inner matrix layer [**claim 1, line 4**] consisting essentially of a mucoadhesive polymer having a mucoadhesive effect [**claim 1, lines 7-8, page 4, lines 26-32**], into which is embedded an active substance which is a peptide or a protein [**claim 1, line 5**], which may include non-natural amino acid residue(s) [**page 7, lines 14-15**],

b) an outer film coating [**claim 1 (b), page 58, lines 15-18; page 4, lines 34 *ff.*]**] consisting essentially of an anionic polymer or copolymer,

wherein said multiparticulate pharmaceutical form is formulated so that the contained pellets are released in the pH range of the stomach [**claim 1, page 58, line 24; page 5, lines 1-3**],

the outer coatings of the pellets are adjusted through the choice of the anionic polymer or copolymer or its formulation with excipients and its layer thickness such that the coating dissolves in pH ranges from 4.0 to 8.0 in the intestine within 15 to 60 min [**claim 1, page 58, lines 26-29; page 5, lines 5-10**], so that the active substance-containing, mucoadhesive

matrix layer is exposed and binds to the intestinal mucosa and releases the active substance there [**claim 1, page 58, lines 31-33; page 5, lines 9-11**],

wherein the active substance content embedded in the matrix layer is a maximum of 40% by weight based on the weight of the polymer having a mucoadhesive effect [**claim 1, page 59, lines 1-3; page 6, lines 29-31**], and

wherein the polymer having a mucoadhesive effect exhibits a mucoadhesive effect of η_b = 150 to 1000 mPa·s [**claim 1, ; page 6, line 23**] and a water uptake of from 10 to 750% in 15 min in a range of +/- 0.5 pH units relative to the pH at which the outer coating starts to dissolve [**claim 1, page 58, lines 34-37; page 6, line 26**] and is selected from the group consisting of at least one of chitosan, a (meth)acrylate copolymer consisting of 20-40% by weight methyl methacrylate and 60 to 80% by weight methacrylic acid, a crosslinked polyacrylic acid, an uncrosslinked polyacrylic acid, an Na alginate, and a pectin [**claim 6, page 60, lines 1-9; page 15-16, including table at top of page 16**] .

Claim 34: A composition containing pellets ranging in size from 50 to 2,500 μm [**claim 1, line 3; page 5, lines 25-30**] that comprise:

a inner matrix comprising 40 wt.% or less of an active pharmaceutical ingredient [**page 5, lines 13-19**] and a polymer having a mucoadhesive effect of at least η_β of 150 to 1,000 mPa·s and a water uptake ranging from 10 to 750% in 15 min at a pH between 5.5 and 7.2 [**page 15, lines 9-35**], and

an outer coating of anionic polymer or anionic copolymer [**page 16, line 6**];

wherein said **particles** do not have a layer separating the inner matrix and outer coating [**claim 18**], and do not have a mucoadhesive lipophilic matrix embedded in the inner matrix [**claim 20; page 34, line 20-page 35, line 31**];

wherein the outer coating dissolves at a pH ranging from 5.5 to 7.2 within 15 to 60 mins [**page 5, lines 7-8; page 6, lines 10-19**].

Claim 33: The oral multiparticulate pharmaceutical form of claim 1 [**as for claim 1 above**], which does not contain gelatin in the inner matrix layer [**Examples, page 43 *ff.***].

(vi) Grounds of Rejection to be Reviewed on Appeal

A. Whether claim 33 lacks adequate written description under 35 U.S.C. 112, first paragraph.

B. Whether claims 1, 3, 6-8, 10, 11 and 34 are obvious under 35 U.S.C. §103(a) over Watts, et al., U.S. Patent No 6,465,626.

C. Whether claims 1 and 4 are obvious under 35 U.S.C. §103(a) over Watts, et al., U.S. Patent No 6,465,626, as applied to claims 1, 3, 6, 7, 8, 10 and 11, and further in view of Berliner, et al., U.S. Patent No. 5,849,327.

D. Whether claims 1, 9 and 10 are obvious under 35 U.S.C. §103(a) over Watts, et al., U.S. Patent No 6,465,626, as applied to claims 1, 3, 6, 7, 8, 10 and 11, and further in view of Engel, et al., U.S. Patent No. 5,773,032.

E. Whether claim 34 is anticipated under 35 U.S.C. §102(b) by Shimono, et al., EP1203590.

F. Whether claims 1 and 33 are obvious under 35 U.S.C. §103(a) over Shimono, et al., EP1203590, in view of Watts, et al., U.S. Patent No. 6,465,626.

(vii) Argument(s)

Issue A: Rejection—35 U.S.C. §112, first paragraph

Claim 33 stands rejected under 35 U.S.C. 112, first paragraph, as lacking adequate written description on the grounds that the disclosure does not describe a composition that does not contain gelatin in its inner matrix layer. Page 6, lines 35 *ff.* disclose the components used to make the inner matrix layer and with the exception of a single mention of gelatin capsules the specification does not use the word "gelatin".

Moreover, the specification exemplifies a composition where the inner matrix does not contain gelatin (see the Examples starting on page 43 of the specification) . The *ipsis verbis* or literal description of a claimed composition is not required so long as it was clear that the Appellants had possession of the invention. A claim term need not be literally described in the specification.

> The test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, **rather than the presence or absence of literal support** in the specification for the claim language (emphasis added)", In re Kaslow, 217 USPQ 1089 (Fed. Cir. 1983).

The disclosure shows that the Appellants possessed the claimed subject matter (compositions containing an inner matrix that does not contain gelatin) since it is actually exemplified in the specification. Accordingly, this rejection cannot be sustained.

Issue B: Rejection—35 U.S.C. §103(a)

Claims 1, 3, 6-8, 10, 11 and 34 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Watts, et al., U.S. Patent No 6,465,626.

The prior art composition of Watts while containing chitosan, also contains a substantial amount of gelatin—a bioadhesive component that preferentially binds to

glycocalyx on a cellular membrane instead of mucus. Independent claim 1 requires an inner matrix "consisting essentially of" mucoadhesive components as well as requires the release of the active substance when the "mucoadhesive matrix layer is exposed and binds to the intestinal mucosa and releases the active substance there".

However, the Watts composition contains a high percentage of gelatin (see Examples 1-4 which incorporate 86.7%, 77.12%, 59.9% and 79.9% gelatin) and would exhibit bioadhesive effects which are disadvantageous compared to the mucoadhesive binding of the invention. The Watts compositions do not specifically target the active ingredient for mucosal release because they are based on usage of substantial quantifies of gelatin as apparent from the title of Watts. "Bioadhesive", for example, refers to binding of the substance to the glycocalyx membrane, but not to the mucus. A bioadhesive composition has the disadvantage of sticking or gluing itself to the intestinal cells via the glycocalyx on their membranes. This causes irritation of the cells or other unwanted pharmacological side-effects. On the other hand, a composition which binds to the mucus, but not directly to the intestinal cells does not suffer from these disadvantages.

The significant amounts of gelatin found in the prior art compositions interfere with the mucoadhesive effect of the multiparticulate composition by adhering directly to intestinal cells and would thus affect the basic and novel characteristics required for the inner matrix layer. Therefore, significant amounts of gelatin (i.e., amounts that interfere with the mucoadhesive effect), such as those present in the prior art compositions, would be excluded by this transitional claim language "consisting essentially of". This transitional claim language excludes ingredients, such as bioadhesive materials, that would affect the basic and novel characteristics of the inner matrix layer which are specifically defined in the claim itself as a "mucoadhesive effect". The quantities of gelatin in the prior art composition interfer with this effect and are excluded. The Examiner asserts that it is unclear what the

differences between a "mucoadhesive" and "bioadhesive" compound are and indicates that both mucus and glycocalyx contain glycoproteins that are presumed to bind to chitosan and gelatin in similar ways. However, the Office has provided no technical reasoning explaining why it believes different compounds, such as chitosan and gelatin that have different chemical structures, equivalently bind to mucus and glycocalyx.

The residence time of mucoadhesives that bind to mucus or mucin differs from the residence time of bioadhesives that bind to cellular membranes. Mucoadhesives are removed by the natural turnover of mucus and thus have lower residence times than bioadhesive compounds like gelatin that bind to cells. Mucus/mucin provides a natural barrier to harmful components. For example, bacteria that are bound by mucus and which do not have bioadhesive properties (e.g., by cell binding proteins, pili, etc.) are washed off the mucosal surface. Similarly, the mucoadhesive properties of the invention limit the residence time of pharmaceutical agents and reduce toxicity and side-effects, while use of corresponding bioadhesive compounds like gelatin increase exposure time and side-effects. The bioadhesive properties of gelatin are described by Shaheen, et al., Int. J. Pharm. 2:504 http://www.ansijournals.com/ijp/2006/504-508.pdf (see Evidence Appendix), see the Introduction which indicates that these bioadhesives bind to mucosal membrane. The present invention is directed to a composition where the inner matrix consists essentially of an active ingredient and a component having a "mucoadhesive effect", while the gelatin of the prior art compositions is a bioadhesive and not mucoadhesive compound. Accordingly, this rejection cannot be sustained.

Issue C: Rejection—35 U.S.C. §103(a)

Claims 1 and 4 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Watts, et al., U.S. Patent No 6,465,626, as applied to claims 1, 3, 6, 7, 8, 10 and 11, and further in view of Berliner, et al., U.S. Patent No. 5,849,327.

Watts does not disclose an inner matrix consisting essentially of a mucoadhesive polymer that targets release of the active component to the mucosa. Berliner was cited as a secondary reference teaching coating thickness, however, it also does not disclose or suggest the mucoadhesive inner matrix of the invention. Thus, this rejection also cannot be sustained since neither document discloses or suggests a composition where the inner matrix consists essentially of an active ingredient (e.g, the elected species of peptidic compound, cetrorelix) and a polymer having a mucoadhesive effect.

Issue D: Rejection—35 U.S.C. §103(a)

Claims 1, 9 and 10 were rejected under 35 U.S.C. §103(a) as being unpatentable over Watts, et al., U.S. Patent No 6,465,626, as applied to claims 1, 3, 6, 7, 8, 10 and 11, and further in view of Engel, et al., U.S. Patent No. 5,773,032.

Watts has been addressed above and does not disclose an inner matrix consisting essentially of a mucoadhesive polymer that targets release of the active component (cetrorelix) to the mucosa. The Watts compositions contain significant amounts of gelatin, a bioadhesive component.

Engel was relied upon as teaching the active ingredient cetrorelix, however, it also does not disclose or suggest the other elements of the invention such as a mucoadhesive inner matrix. Moreover, none of the prior art suggests or provides a reasonable expectation of success that the elected species cetrorelix would be compatible with the other components of the invention and be released as required by claim 1. Therefore, this rejection cannot be sustained.

Issue E: Rejection—35 U.S.C. §102

Claim 34 stands rejected under 35 U.S.C. §102(b) as being anticipated by Shimono, et al., EP1203590. Claim 34, as it reads on the elected species, is not anticipated by Shimono since Shimono does not disclose cetrorelix or an active peptidic substance embedded in the inner matrix layer. The compositions exemplified by Shimono contain acetaminophen a non-peptide drug and while the specification generically refers to a "medicament", this is insufficient to disclose the elected species under examination with sufficient specificity to anticipate the invention.

Shimono also uses chitosan only in combination with a water-insoluble polymer having a chitosan powder dispersed therein. Thus, after dissolution of the enteric coating this mixture will take a long time to dissolve because of the water-insolubility of the coating. The chitosan will be released very slowly and thus will be spread over a large area of the intestine. This is quite different than the invention which provides immediate chitosan exposure which binds a specific target in a defined area of the mucosa.

Moreover, the Shimono construct does not conform to the invention under examination. Claim 34 on appeal (in accord with the election of species requirement) requires that there is no layer separating the inner matrix containing the cetrorelix and the outer coating. However, the water insoluble polymer layer (1, see abstract) of Shimono that contains chitosan particles separates the non-pareil layer (the "medicament-containing solid material", see abstract) containing the medicament/acetaminophen from the outer enteric polymer coating (2, see abstract). See also, Example 1 on page 11, top of col. 1 which shows that the chitosan layer separates the acetaminophen-containing layer from the enteric coating.

Furthermore, the chitosan particles in the Shimono composition act as "pore forming" agent in the large intestine [0039] and not as a mucoadhesive component of an inner matrix layer as required by the present claims. Accordingly, this rejection cannot be sustained.

Issue F: Rejection—35 U.S.C. §103

Claims 1 and 33 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Shimono, et al., EP1203590, in view of Watts, et al., U.S. Patent No. 6,465,626. Shimono ands Watts in combination do not disclose all the elements of the invention under examination and, therefore, cannot render the claimed invention obvious.

Watts is specifically directed to "Pharmaceutical compositions of chitosan with type-A gelatin", see the title. Claim 33 from the core and claim 1 excludes it because it is not a mucoadhesive ingredient. The Office has provide no evidence that gelatin is such a mucoadhesive ingredient and has not provide evidence rebutting the Appellants' explanation of the differences between a mucoadhesive component like chitosan, and a bioadhesive component such as gelatin. Watts does not disclose the elected species of active ingredient cetrorelix.

Shimono requires an insoluble polymer layer containing chitosan particles that separates the acetaminophen-containing non-pareil core from the enteric coating. The elected species of invention subject to examination does not contain this layer. Moreover, Shimono does not disclose the other elected subject matter including the active peptidic component of the inner matrix, cetrorelix.

Neither Watts nor Shimono discloses cetrorelix and therefore this rejection does not make a *prima facie* case for the obviousness of the elected species under examination. Moreover, neither document discloses an inner matrix core "consisting essentially of" the active ingredient and a mucoadhesive polymer. Therefore, this rejection cannot be sustained.

RELIEF REQUESTED

The Appellants respectfully request the REVERSAL of the grounds of rejection above.

Respectfully submitted,

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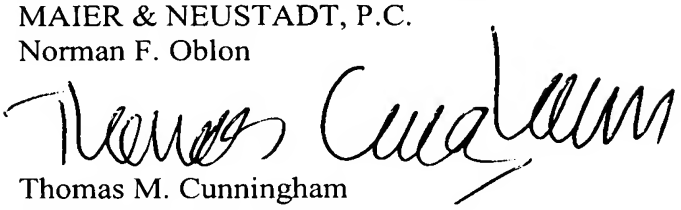

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(viii) Claims Appendix

Claim 1 (Previously Presented): An oral multiparticulate pharmaceutical form comprising pellets having a size in the range from 50 to 2,500 μm, which comprise:

a) an inner matrix layer consisting essentially of a mucoadhesive polymer having a mucoadhesive effect, into which is embedded an active substance which is a peptide or a protein, which may include non-natural amino acid residue(s),

b) an outer film coating consisting essentially of an anionic polymer or copolymer,

wherein said multiparticulate pharmaceutical form is formulated so that

the contained pellets are released in the pH range of the stomach,

the outer coatings of the pellets are adjusted through the choice of the anionic polymer or copolymer or its formulation with excipients and its layer thickness such that the coating dissolves in pH ranges from 4.0 to 8.0 in the intestine within 15 to 60 min, so that the active substance-containing, mucoadhesive matrix layer is exposed and binds to the intestinal mucosa and releases the active substance there,

wherein the active substance content embedded in the matrix layer is a maximum of 40% by weight based on the weight of the polymer having a mucoadhesive effect, and

wherein the polymer having a mucoadhesive effect exhibits a mucoadhesive effect of η_b = 150 to 1000 mPa·s and a water uptake of from 10 to 750% in 15 min in a range of +/- 0.5 pH units relative to the pH at which the outer coating starts to dissolve and is selected from the group consisting of at least one of chitosan, a (meth)acrylate copolymer consisting of 20-40% by weight methyl methacrylate and 60 to 80% by weight methacrylic acid, a crosslinked polyacrylic acid, an uncrosslinked polyacrylic acid, an Na alginate, and a pectin.

Claim 2 (Withdrawn): The oral multiparticulate pharmaceutical form of claim 1, wherein the outer film coating is at least one material selected from the group consisting of

cellulose glycolate (Duodcell®), cellulose acetate phthalate (CAP, Cellulosi acetas, PhEur, cellulose acetate phthalates, NF, Aquaterie®), cellulose acetate succinate (CAS), cellulose acetate trimeliate (CAT), hydroxypropylmethylcellulose phthalate (HPMCP, HP50, HP55), hydroxypropylmethylcellulose acetate succinate (HPMCAS-LF, -MF, -HF), polyvinyl acetate phthalate (PVAP, Sureteric®), vinyl acetate-vinylpyrrolidone copolymer (PVAc, Kollidon® VA64), vinyl acetate:crotonic acid 9:1 copolymer (VAC:CRA, Kollicoat® VAC) and shellack.

Claim 3 (Previously Presented): The oral multiparticulate pharmaceutical form of claim 1, wherein the outer film coating consists of a (meth)acrylate copolymer having a content of monomers having anionic groups of from 5 to 60% by weight.

Claim 4 (Previously Presented): The oral multiparticulate pharmaceutical form of claim 1, wherein the layer thickness of the outer coating is in the range from 20 to 200 μm.

Claim 5 (Withdrawn): The oral multiparticulate pharmaceutical form of claim 1, further comprising a protease inhibitor and/or a penetration promoter.

Claim 6 (Previously Presented): The oral multiparticulate pharmaceutical form of claim 1, wherein the mucoadhesive polymer in the inner matrix is chitosan and the active pharmaceutical ingredient comprises Cetrorelix; and the outer coating comprises a copolymer of 50 wt% methylmethacrylate and 50 wt% methacrylic acid.

Claim 7 (Previously Presented): The oral multiparticulate pharmaceutical form of claim 6, wherein the inner matrix contains as polymer having a mucoadhesive effect a

chitosan which is employed together with an acid or a buffer system, which is located in the matrix or in or on a core onto which the matrix is applied.

Claim 8 (Previously Presented): The oral multiparticulate pharmaceutical form of claim 7, wherein the inner matrix layer contains chitosan and is adjusted to pH 5.0 to 5.5 by means of an acid or a buffer system, and is combined with an outer film coating which starts to dissolve in the range from pH 6.0 to 8.0.

Claim 9 (Previously Presented): The oral multiparticulate pharmaceutical form of claim 1, wherein the active substance is a protein or a peptide having an average molecular weight M_w of less than 3,000 Da.

Claim 10 (Previously Presented): The oral multiparticulate pharmaceutical form of claim 9, wherein the active substance is selected from the group consisting of abarelix angiogenesis II, anidulafungin, antide, argipressin, azaline and azaline B, bombesin antagonist, bradykinin, buserelin, cetrorelix, cyclosporin A, desmopressin, detirelix, encephalins (Leu-, Met-) ganirelix, gonadorelin, goserelin, growth hormone secretagogue, micafungin, nafarelin, leuprolide, leuprorelin, octreotide, orntide, oxytocin, ramorelix, secretin, somatotropin, terlipressin, tetracosactide, teverelix, triptorelin, thyroliberin, thyrotropin, vasopressin and mixtures thereof.

Claim 11 (Withdrawn): The oral multiparticulate pharmaceutical form of claim 9, wherein the inner matrix layer additionally contains a C_6- to C_{20}-fatty acid and/or a C_6- to C_{20}-alcohol including their salts, ether, ester or amide derivatives and/or a lipid and/or a phospholipid and/or a lipid-soluble vitamin.

Claim 12 (Withdrawn): The oral multiparticulate pharmaceutical form of claim 1, wherein the active substance is a protein or peptide having an average molecular weight M_w of from 3,000 to 10,000.

Claim 13 (Withdrawn): The oral multiparticulate pharmaceutical form as claimed in claim 12, wherein the active substance is at least one substance selected from the group consisting of calcitonin, corticotrophin, endorphins, epithelial growth factor, glucagon, insulin, novolin, parathyroid hormone, relaxin, pro-somatostatin and salmon secretin.

Claim 14 (Withdrawn): The oral multiparticulate pharmaceutical form as claimed in claim 12 wherein the matrix layer comprises a C_6- to C_{20}-alcohol including their salts, ether, ester or amide derivatives and/or a lipid and/or a phospholipid and/or a lipid-soluble vitamin and/or a protease inhibitor.

Claim 15 (Withdrawn): The oral multiparticulate pharmaceutical form of claim 1, wherein the active substance is a protein or peptide having an average molecular weight M_w of more than 10,000.

Claim 16 (Withdrawn): The oral multiparticulate pharmaceutical form as claimed in claim 15, wherein the active substance is at least one substance selected from the group consisting of interferon (alpha, beta, gamma), interleukins (IL1, IL2), somatotropin, erythropoietin, tumor necrosis factor (TNF alpha, beta), relaxin, endorphin, dornase alpha, follicle stimulating hormone (FSH), human chorionic gonadotropin (HCG), human growth hormone release factor (hGRF), luteinizing hormone (LH) and epidermal growth factor.

Claim 17 (Withdrawn): The oral multiparticulate pharmaceutical form as claimed in claim 15 wherein the matrix layer comprises a C_6- to C_{20}-fatty acid and/or a C_6- to C_{20}-alcohol including their salts, ether, ester or amide derivatives and/or a lipid and/or a phospholipid and/or a lipid-soluble vitamin and/or a protease inhibitor and/or a penetration promoter.

Claim 18 (Withdrawn): The oral multiparticulate pharmaceutical form as claimed in claim 1, wherein a separating layer is applied between the active substance-containing matrix layer and the outer film coating layer.

Claim 19 (Withdrawn): A process for producing an oral multiparticulate pharmaceutical form as claimed in claim 1, comprising

a) producing an inner matrix layer comprising an active substance, which is a peptide or a protein, and a polymer having a mucoadhesive effect and, where appropriate, further pharmaceutically usual excipients by means of spray application onto a core or by rotagglomeration, precipitation or spray processes without a core, and subsequently,

b) applying an outer film coating consisting essentially of an anionic polymer or copolymer, which may optionally be formulated with pharmaceutically usual excipients, especially plasticizers, by means of spray application so that active substance-containing, enveloped pellets are obtained, and

c) processing the resulting pellets by means of pharmaceutically usual excipients in a manner known per se to a multiparticulate pharmaceutical form, in particular to pellet-containing tablets, minitablets, capsules, sachets or reconstitutable

powders, which are formulated so that the contained pellets are released in the pH range of the stomach.

Claim 20 (Withdrawn): The oral multiparticulate pharmaceutical form as claimed in claim 1, wherein the active substance is embedded in a lipophilic matrix which has a melting point above 37°C, and the active substance-containing lipophilic matrix is embedded in the matrix composed of the polymer having a mucoadhesive effect.

Claim 21 (Withdrawn): The oral multiparticulate pharmaceutical form as claimed in claim 20, wherein the active substance and the substance or substances forming the lipophilic matrix differ in their solubility in water according to DAB 10 and not more than +/- 50%, and/or differ in their partition coefficient according to annex V to directive 67/548/EEC, A.8 by not more than +/- 60%, and/or differ in their HLB measured by the method of Marszall not more +/- 80%.

Claim 22 (Withdrawn): The oral multiparticulate pharmaceutical form as claimed in claim 20, wherein an active substance which has a solubility in water according to DAB 10 of at least 30 parts by volume of water for one part by weight of active substance is present.

Claim 23 (Withdrawn): The oral multiparticulate pharmaceutical form as claimed in claim 22, wherein the active substance is at least one substance selected from the group consisting of peptide antibiotics, immunosuppressants, LHRH antagonists and immunomodulators.

Claim 24 (Withdrawn): The oral multiparticulate pharmaceutical form as claimed in claim 22, wherein the active substance is at least one substance selected from the group consisting of abarelix, angiotensin II, anidulafungin, antide, argipressin, azaline and azaline B, bombesin antagonist, bradykinin, buserelin, calcitonin, cetrorelix, cyclosporin, cyclosporin A, desmopressin, detirelix, erythropoietin, encephalins (Leu-, Met-) ganirelix, gonadorelin, goserelin, growth hormone secretagogue, insulin, interferon (alpha, beta, gamma), interleukins (IL1, IL2), micafungin, nafarelin, leuprolide, leuprorelin, octreotide, orntide, oxytocin, parathyroid hormone, ramorelix, secretin, somatotropin, terlipressin, tetracosactide, teverelix, triptorelin, thyroliberin, thyrotropin, tumor necrosis factor (TNF alpha, beta) and vasopressin.

Claim 25 (Withdrawn): The oral multiparticulate pharmaceutical form as claimed in claim 20, wherein the substance or substances forming the lipophilic matrix, and the polymer having a mucoadhesive effect either have the same ionic property or, in the event of opposed ionic properties, the polymer having a mucoadhesive effect is present in at least 50% neutralized form.

Claim 26 (Withdrawn): The oral multiparticulate pharmaceutical form as claimed in claim 20, wherein the lipophilic matrix consists of 80 to 100% by weight of a substance having an HLB of from 0 to 15 or of a mixture of substances having an average HLB of from 0 to 15, and may comprise from 0 to 20% by weight of pharmaceutically usual excipients, stabilizers, thickeners or adsorbents.

Claim 27 (Withdrawn): The oral multiparticulate pharmaceutical form as claimed in claim 20, wherein the substance or the substances forming the lipophilic matrix are at least

one substance selected from the group consisting of oils, fats, mono-, di- or triglycerides, fatty acids, fatty alcohols, especially C_6 to C_{20}-fatty acid and/or a C_6- to C_{20}- alcohol including their salts, ether, ester or amide derivatives, phospholipids, lecithins, emulsifiers, lipoids, lipid-soluble vitamins and surfactants.

Claim 28 (Withdrawn): The oral multiparticulate pharmaceutical form as claimed in claim 20, wherein the lipophilic matrix comprises one of the following lipid preparations: (Imwitor 308) glyceryl monocaprylates having a monoester content of > 80%, (Imwitor 312) glyceryl monolaurates having a monoester content of > 90%, (Imwitor 491) glycerol monostearates (C_{16} + C_{18}) having a monoester content of > 90%, (Imwitor 900 P) glycerol monostearate having a monoester content of 40-55% and a C_{18} content of 40-60%, (Imwitor 900 K) glycerol monostearate, having a monoester content of 40-55% and a C_{18} content of 60-80%, (Imwitor 742) medium chain-length C_8 and C_{10} glycerides having a monoester content of 45-55%, (Imwitor 928) partial glycerides of saturated vegetable C_{10}-C_{18} fatty acids having a main content of C_{12}, and having a monoester content of 34-36%, C_8 and C_{10} glycerides, Na caprylate or Na capriate.

Claim 29 (Withdrawn): The oral multiparticulate pharmaceutical form as claimed in claim 20, wherein the active substance is at least 10% soluble in the lipophilic matrix.

Claim 30 (Withdrawn): The oral multiparticulate pharmaceutical form as claimed in claim 20, wherein the content of active substance-containing lipophilic matrix in the inner matrix layer a) is from 5 to 50% by weight.

Claim 31 (Withdrawn): A process for producing an oral multiparticulate pharmaceutical form as claimed in claim 20, comprising

a) producing the active substance-containing lipophilic matrix by suspending and/or dissolving the active substance with the substance(s) which form the lipophilic matrix and, where appropriate, further pharmaceutically usual excipients by vigorously mixing or melting the ingredients,

b) producing pre-pellets (pellet cores) by spray application of the mucoadhesive polymer mixed with the active substance-containing lipophilic matrix onto a core or by rotagglomeration, precipitation or spray processes without a core,

c) producing pellets by spray application of a coating of the anionic polymer or copolymer, which may optionally comprise admixtures of pharmaceutically usual excipients, especially plasticizers and release agents, from a dispersion or organic solution onto the pre-pellets from step b),

d) producing a multiparticulate pharmaceutical form by filling or incorporating the pellets from step c) in a manner known per se, where appropriate with use of pharmaceutically usual excipients, in particular by processing to pellet-containing tablets, minitablets, capsules, sachets or reconstitutable powders.

Claim 32 (Withdrawn): The process for producing an oral multiparticulate pharmaceutical form as claimed in claim 31, wherein steps a) and b) comprise

a) producing the inner matrix layer by preparing an emulsion, dispersion or solution of the active substance with the substance(s) for the lipophilic matrix, and where appropriate further pharmaceutically usual excipients by vigorously mixing the ingredients in water and producing an oil-in-water preparation having an average particle size of not more than 60 μm,

b) producing pre-pellets by spray application of the oil-in-water preparation from step a) onto the mucoadhesive polymer which may optionally comprise admixtures of further pharmaceutically usual excipients, where the ingredients are in the form of a micronized powder, by rotagglomeration, extrusion or granulation.

Claim 33 (Previously Presented): The oral multiparticulate pharmaceutical form of claim 1, which does not contain gelatin in the inner matrix layer.

Claim 34 (Previously Presented): A composition containing pellets ranging in size from 50 to 2,500 μm that comprise:

a inner matrix comprising 40 wt.% or less of an active pharmaceutical ingredient and a polymer having a mucoadhesive effect of at least η_β of 150 to 1,000 mPa·s and a water uptake ranging from 10 to 750% in 15 min at a pH between 5.5 and 7.2, and

an outer coating of anionic polymer or anionic copolymer;

wherein said particles do not have a layer separating the inner matrix and outer coating, and do not have a mucoadhesive lipophilic matrix embedded in the inner matrix;

wherein the outer coating dissolves at a pH ranging from 5.5 to 7.2 within 15 to 60 mins.

Claim 35 (Previously Presented): The composition of claim 34, wherein the mucoadhesive inner matrix comprises:

chitosan and the active pharmaceutical ingredient comprises Cetrorelix; and

the outer coating comprises a copolymer of 50 wt% methylmethacrylate and 50 wt% methacrylic acid.

(ix) Evidence Appendix

Shaheen, et al., Int. J. Pharm. 2:504, http://www.ansijournals.com/ijp/2006/504-508.pdf.

(x) Related Proceedings Appendix

(None)

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Effect of Bio-adhesive Polymers like HPMC, Gelatin, Na-CMC and Xanthan Gum on Theophylline Release from Respective Tablets

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Abstract: In order to evaluate the feasible application of bio-adhesive polymers like HPMC-15 cps and 50 cps; gelatin; Na-CMC and xantham gum in sustained release dosage form (SRDF), tablets containing various amount of bio-adhesive polymers with a model drug like anhydrous Theophylline sodium glycinate were prepared by compression in a hydraulic press (Perkin Elmer) compression machine using 5 ton pressure. The release characteristics of Theophylline (TH) from sustained release tablets were analyzed in triplicate using a thermal shaker (Memmert) with a shaking speed of 50 rpm at 37±0.5°C in 250 mL of simulated gastric fluid without enzyme for 8 h. At the end of 8 h of dissolution it was found that 61.60% (for 300 mg HPMC-15 cps) and 42.92% (for 500 mg HPMC-15 cps) of TH was released from HPMC-15 cps based tablets, respectively. When HPMC-15cps was increased to 50 cps, 52.12 and 59.66% of TH was released, respectively. Both concentration and viscosity depended sustained release of TH was found. 74.13 and 94.15% of TH was released from Gelatin based SR tablets of the same concentrations, respectively. Gelatin also showed the same concentration effects i.e. release was reduced with an increase in concentration of polymer. 52.40 and 50.95% of TH was released from Na-CMC based SR tablets of the same concentrations, respectively and that of 76.96 and 78.26% of TH from xanthan gum based tablets. It means that there was no remarkable concentration effect of these two polymers on the TH release. In all cases there was almost zero order release fashion. Bio-adhesive polymers like HPMC and gelatin might be successfully applicable in SRDF rather than Na-CMC and xanthan gum studied here.

Key words: Bio-adhesive polymer, sustained release, dissolution, theophylline

INTRODUCTION

The term bio-adhesive describes materials that bind to biological substrate such as, mucosal membrane. Adhesion of bio-adhesive drug delivery devices to mucosal membrane leads to an increased drug concentration gradient at the absorption site and therefore improved bioavailability of systematically delivered drugs (Hannah, 2004). In general terms, adhesion of polymers to tissues may be achieved by (i) physical or mechanical bonds, (ii) primary or covalent chemical bonds and/or (iii) secondary chemical bonds (i.e., ionic). Physical or mechanical bonds can result from deposition and inclusion of the adhesive material in the crevices of the mucus or the folds of the mucosa. Secondary chemical bonds, contributing to bio-adhesive properties, consist of dispersive interactions (i.e., Van der Waals interactions) and stronger specific interactions, which include hydrogen bonds. The hydrophilic functional groups responsible for forming hydrogen bonds are the hydroxyl (--OH) and the carboxylic groups (--COOH). Adhesive microspheres have been selected on the basis of the physical and chemical bonds formed as a function of chemical composition and physical characteristics, such as surface area.

This invention relates to a bio-adhesive tablet containing at least one bio-adhesive adjuvant and at least one lubricant, with at least one surface of the tablet comprising concentric or parallel, straight and/or curved depressions and to a method for producing the bioadhesive tablets as well as to pharmaceuticals in the form of the bioadhesive tablets. The bioadhesive tablets of the invention nearly completely release the active agent they contain and stimulate its resorption by the tissue while not entering into any undesirable with the biological tissue.

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The bioadhesive adjuvant should preferably be a substance that develops adhesion when coming into contact with the mucosa, such as hydroxypropyl methylcellulose (HPMC-15 and 50 cps), Sodium carboxymethyl cellulose (Na-CMC), gelatin, Xanthan gum. It is furthermore considered advantageous that the lubricant facilitates tabletting of cohesive mixtures as do talc, Mg-stearate.

The bio-adhesive tablets of the invention can be produced in a known way. Any active agent, especially medicinal substances, can be molded into tablets that adhere to the mucosa by adding a bioadhesive adjuvant, a lubricant and optionally other adjuvant common in tabletting using a simple technique. In the organism, the bioadhesive tablet is to adhere to the mucosa immediately upon contacting it, to develop as large a contact area as possible with the mucosa, while containing exclusively toxicologically safe adjuvants .

Xanthan gum, a hydrophilic polymer, was added to the formulation to increase the drug release. Changing the xanthan gum concentration as well as its particle size modified the *in vitro* drug release. Increasing xanthan gum concentrations yielded a faster drug release due to a higher liquid uptake, swelling and erosion rate (Verhoeven *et al.*, 2006).

Gelatin is a thermoreversible or cold-setting polymer. If the gelatin is not refrigerated or reheated, it will slowly convert back to a liquid. Because of this, a gelatin such as Jell-O® should remain refrigerated or it will become tasteless Kool-Aide®. Another popular dessert is Jell-O® instant pudding. It contains a modified food starch instead of gelatin. The instant pudding uses a heat-setting super absorbing thickening polymer (the starch) to create its gelatinous texture (PSLC, 2003). Gelatin and dextran were reported to blended and cross-linked hydrogels to form enzymatically degradable interpenetrating polymeric networks (IPNs) as materials for degradable implants (Kosmala *et al.*, 2000).

It was reported that a study of the erosion rates of matrices containing only indicated that Na-CMC (Belanose) eroded more quickly than HPMC (Dabbagh *et al.*, 1999).

Effect of incorporating pharmaceutical excipients on the in vitro release profiles and the release mechanism of monolithic hydroxypropylmethylcellulose (4000 cps) matrix tablets (m-HPMC tablets) in terms of mimicking the dual drug release character of bi-layered Tylenol ER tablets was studied. Release profiles and swelling rates of m-HPMC tablets were found to be highly influenced by the types and amounts of pharmaceutical excipients incorporated. The effect of pharmaceutical excipients on drug release from HPMC-based matrix tablets was found to be mainly due to a change in hydrophilic gel expansion and on physical interactions between the drug and HPMC (Cao *et al.*, 2005).

MATERIALS AND METHODS

Materials: Theophylline Na-Glycinate was a gift sample from Square Pharmaceuticals Bangladesh Limited. Sodium carboxymethylcellulose (Na-CMC), Xanthan gum, Gelatin and hydroxypropyl methylcellulose (HPMC, having a viscosity of 15 cps and 50 cps), were purchased from Loba Chemie Pvt. Ltd., India. Sodium chloride (Loba Chemie Pvt. Ltd., India.) were procured from commercial source. All other reagent used was of analytical grade.

Methodology: For tablet preparation, the amount of active ingredient is 100 mg and the total weight of tablet content was 406 and 609 mg. Theophylline Na-Glycinate, HPMC-15 and 50 cps, gelatin, Na-CMC, xanthan gum as a single bio-adhesive polymer, aerosil and Mg-Stearate were weighed separately (for 20 tablets) according to the formulations in Table 1 using a Mettler balance (AE--50, Switzerland) and mixed thoroughly in a drum blender mounted angularly ensuring thorough mixing. From this mixed mass, amount for individual tablet was weighed out and compressed into tablets in a hydraulic press (Perkin Elmer) compression machine using 5 ton pressure. Before compression, the surface of the die and punch was lubricated with magnesium stearate.

Table 1: The features of matrix tablets

Tablet code	No. of tablets	Drug (mg)	HPMC (15 cps) (mg)	HPMC (50 cps) (mg)	Gelatin (mg)	Na-CMC (mg)	Xanthan Gum (mg)	Aerosil (mg)	Mg. stearate	Total weight (mg)
F-1	20	100	300	-	-	-	-	4	2	406
F-1(a)	20	100	-	300	-	-	-	4	2	406
F-2	20	100	-	-	300	-	-	4	2	406
F-3	20	100	-	-	-	-	-	4	2	406
F-4	20	100	-	-	-	300	-	4	2	406
F-5	20	100	-	-	-	-	300	4	2	406
F-6	20	100	500	-	-	-	-	5	4	609
F-6(a)	20	100	-	500	-	-	-	5	4	609
F-7	20	100	-	-	500	-	-	5	4	609
F-8	20	100	-	-	-	-	-	5	4	609
F-9	20	100			-	500	-	5	4	609
F-10	20	100	-	-	-	-	500	5	4	609

***In vitro* dissolution study of tablets:** The release characteristics of Theophylline Na-Glycinate from sustained release tablets were supplied in triplicate using a thermal shaker (Memmert) with a shaking speed of 50 rpm at 37±0.5°C in 250 mL of simulated gastric fluid for 8 h. The dissolution samples were collected at a given interval (30 min), replaced with an equal volume of gastric fluid. The concentration of Theophylline Na-Glycinate release as a function of time was determined using an UV spectrophotometer (Shimadzu, Japan) at λ_{max}. 271 nm.

Standard curve preparation: Standard Theophylline Na-Glycinate solution was prepared in the concentration range of 2-20 μg mL^{-1}. Then the absorbance of the standard solution of the different concentration were observed in the UV visible spectrophotometer (UV-1601, SHIMADZU, Japan) at λ_{max} 271 nm. From the observed absorbance, standard calibration curve was made for the assay of Theophylline Na-glycinate.

RESULTS AND DISCUSSION

Various theories have been elaborated in order to describe the process of release of the drug from matrices, by considering either diffusion (Armand *et al.*, 1987), in the case of non-erodable polymers, or erosion with erodable polymers (Bidah and Vergnaud, 1990).

Standard or working curve: A straight line was found when absorbance was plotted against concentration (Fig. 1). The slope value was found out from this straight line and used to calculate the drug concentration with proper volume corrections.

Effect of polymer (HPMC-15 cps) on the release of Theophylline from F-1 and F-6: The release profiles of Theophylline from F-1 and F-6 were shown in Fig. 2. F-1 contains 300 mg of HPMC-15 cps and F-6 contains 500 mg of HPMC-15 cps. About 5.81 and 1.52% of Theophylline released from F-1 and F-6, respectively after 30 min of dissolution period. After 4 h of dissolution period F-1 and F-6 released 38.32 and 20.08% of Theophylline respectively. At the end of 8 h of dissolution it was found that 61.60 and 42.92% of Theophylline have been released from F-1(a) and F-6(a) respectively. HPMC-15 cps is a hydrophilic gel forming agents. It is preferred the formulators to modulate drug release mainly due to its claim to form strong viscous gel in contact with water. It has been observed that the release of Theophylline decreased when the amount of polymer increased.

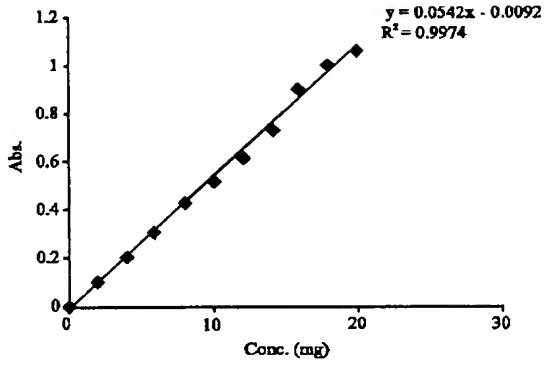

Fig. 1: Standard curve of theophylline Na-glycinate

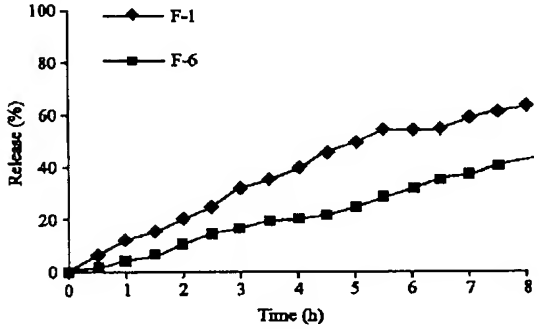

Fig. 2: Theophylline release profiles from HPMC-15 cps based tablets

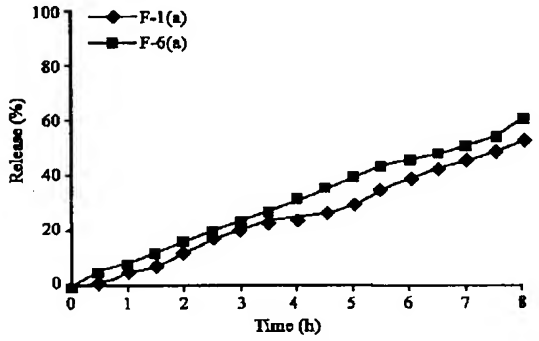

Fig. 3: Theophylline release profiles from HPMC-50 cps based tablets

Effect of polymer (HPMC-50 cps) on the release of Theophylline from F-1(a) and F-6(a): Tablets of F-1(a) and F-6(a) were prepared by the same process as described earlier. The release profiles of Theophylline from F-1(a) and F-6(a) were shown in Fig. 3. F-1(a) contains 300 mg of HPMC-50 cps and F-6(a) contains 500 mg of HPMC-50 cps. About 1.19 and 5.46% of Theophylline released from F-1(a) and F-6(a), respectively after 30 min of dissolution

period. After 4 h of dissolution period, F-1(a) and F-6(a) released 23.84 and 31.81% of Theophylline, respectively. At the end of 8 h of dissolution it was found that 52.12 and 59.66% of Theophylline have been released from F-1(a) and F-6(a), respectively.

Effect of polymer (Gelatin) on the release of Theophylline from F-2 and F-7: Tablets of F-2 and F-7 were prepared by the same process as described earlier The release profiles of Theophylline from F-2 and F-7 were shown in Fig. 4. F-2 contains 300 mg of Gelatin and F-7 contains 500 mg of Gelatin. About 1.43 and 3.33% of Theophylline released from F-2 and F-7, respectively after 30 min of dissolution period. After 4 h of dissolution period F-2 and F-7 released 57.87 and 69.14% of theophylline, respectively. At the end of 8 h of dissolution, it was found that 74.13 and 94.15% of theophylline have been released from F-2 and F-7, respectively.

Effect of polymer (Na-CMC) on the release of Theophylline from F-4 and F-9: Tablets of F-4 and F-9 were prepared by the same process as described earlier The release profiles of Theophylline from F-4 and F-9 were shown in Fig. 5. F-4 contains 300 mg of Na-CMC and F-9 contains 500 mg of Na-CMC. About 0.59 and 2.73% of Theophylline released from F-4 and F-9, respectively after 30 min of dissolution period. After 4 h of dissolution period F-4 and F-9 released 27.12 and 27.72% of Theophylline, respectively. At the end of 8 h of dissolution, it was found that 52.40 and 50.95% of Theophylline have been released from F-4 and F-9, respectively.

Effect of polymer (xanthan gum) on the release of Theophylline from F-5 and F-10: Tablets of F-5 and F-10 were prepared by the same process as described earlier. The release profiles of Theophylline from F-5 and F-10 were shown in Fig. 6. F-5 contains 300 mg of xanthan gum and F-6 contains 500 mg of Xanthan gum. About 1.19 and 3.99% of theophylline released from F-5 and F-10, respectively after 30 min of dissolution period. After 4 h of dissolution period F-5 and F-10 released 46.27 and 40.67% of theophylline, respectively. In case of F-10 after 6 h of dissolution period there is a vast release of active ingredient. At the end of 8 h of dissolution, it was found that 76.96 and 78.26% of Theophylline have been released from F-5 and F-10, respectively. It has been observed that there was no significant effect of drug release for the increase of polymer.

Release fashion: In almost all cases the release fashion i.e., % release vs. time curves were approximately straight lines, which approximates to the zero order release fashion.

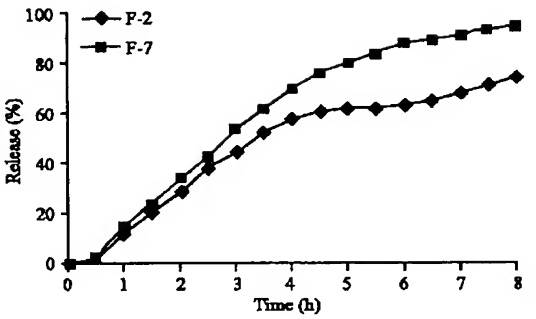

Fig. 4: Theophylline release profiles from gelatin based tablets

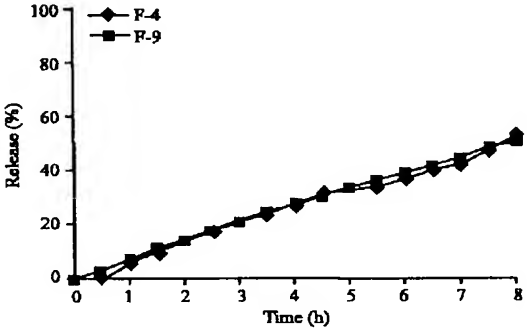

Fig. 5: Theophylline release profiles from Na-CMC based tablets

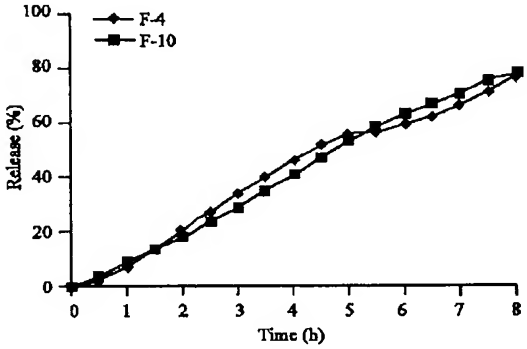

Fig. 6: Theophylline release profiles from xanthan gum based tablets

CONCLUSIONS

Bio-adhesive polymers like HPMC, Gelatin, Na-CMC and Xantham gum were evaluated in sustaining the drug release from their respective tablets. Both the HPMC showed the concentration as well as grade-dependent sustained release of TH. Gelatin also showed

concentration dependent TH release whereas Na-CMC and Xantham gum showed a very little dependency with sustaining the TH release. In all cases the release fashion was approximately zero order process. The potential application of HPMC with their different grades and Gelatin might be feasible in SRDF.

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